

Amendments to the Claims:

The following listing of claims shall replace all prior version and listings of claims in this application.

Listing of Claims:

We claim:

Claims 1-61 (Canceled)

Claim 62. (Currently Amended) A method for producing a non-human transgenic mammal, the method comprising:

- (a) modifying the nuclear genome of a fibroblast cell that has a sufficient lifespan to be useful for genetic modification, wherein the genome has a normal karyotype, at an endogenous locus ~~by homologous recombination~~;
- (b) transferring the modified nuclear genome of the fibroblast cell to an oocyte, two cell embryo or zygote all of which have been enucleated which is capable of producing a viable nuclear transfer unit;
- (c) activating the nuclear transfer unit thereby producing an embryo;
- (d) transferring the embryo to a final surrogate mother which is a suitable host for the mammal to be grown to term; and
- (e) allowing the embryo to develop to term, thereby producing a non-human transgenic mammal.

Claim 63 (Previously Presented) The method of claim 62, wherein the transgenic mammal is a transgenic sheep, cattle, goat, pig, horse, camel, rabbit or rodent.

Claim 64 (Canceled)

Claim 65 (Currently Amended) The method of claim 62, wherein the ~~modification homologous recombination~~ results in removal of a gene, modification of a gene, upregulation of a gene, gene replacement or transgene placement.

Claim 66 (Currently Amended) The method of claim 62, wherein the ~~modification homologous recombination~~ results in inactivation of a gene.

Claim 67-72 (Canceled)

Claim 73 (Currently Amended) The method of claim 145 70, wherein the promoter directs expression of at least one gene in fibroblast cells.

Claim 74 (Canceled)

Claim 75 (Previously Presented) The method of claim 62, wherein the modification comprises placing a marker gene at the endogenous locus in the nuclear genome.

Claim 76 (Previously Presented) The method of claim 75, wherein the marker gene is a gene that confers resistance to a drug.

Claim 77 (Previously Presented) The method of claim 76, wherein the gene that confers resistance to a drug is selected from the group consisting of neomycin, G418, hygromycin, zeocin, blasticidin and histidinol.

Claim 78 (Previously Presented) The method of claim 75, wherein the marker gene is selected from the group consisting of HPRT, gpt, a visible marker gene and a gene that can be detected with a single chain antibody/hapten system.

Claim 79 (Previously Presented) The method of claim 78, wherein the visible marker gene is GFP.

Claim 80-81 (Canceled)

Claim 82 (Currently Amended) The method of claim 62, wherein the modification homologous recombination is mediated by lipofection.

Claim 83-86 (Canceled)

Claim 87 (Previously Presented) The method of claim 62, wherein the cell is an epithelial cell, a fibroblast cell, an endothelial cell or a muscle cell.

Claim 88 (Previously Presented) The method of claim 62, wherein the cell is a G₀ cell.

Claim 89 (Previously Presented) The method of claim 88, wherein the G₀ cell is obtained by serum starvation of a cell.

Claim 90 (Currently Amended) A method for producing transgenic offspring from a transgenic mammal, the method comprising:

- (a) modifying the nuclear genome of a fibroblast cell that has a sufficient lifespan to be useful for genetic modification, wherein the genome has a normal karyotype, at an endogenous locus ~~by homologous recombination~~;
- (b) transferring the modified nuclear genome of the fibroblast cell to an oocyte, two cell embryo or zygote all of which have been enucleated which is capable of producing a viable nuclear transfer unit;
- (c) activating the nuclear transfer unit thereby producing an embryo;
- (d) transferring the embryo to a final surrogate mother which is a suitable host for the mammal to be grown to term;

- (e) allowing the embryo to develop to term, thereby producing a non-human transgenic mammal; and
- (f) breeding the transgenic mammal to produce transgenic offspring from the transgenic mammal.

Claim 91-98 (Canceled)

Claim 99 (Currently Amended) The method of claim 90, wherein the modification homologous recombination results in removal of a gene, modification of a gene, upregulation of a gene, gene replacement or transgene placement.

Claim 100 (Currently Amended) The method of claim 90, wherein the modification homologous recombination results in inactivation of a gene.

Claim 101 (Canceled)

Claim 102 (Previously Presented) The method of claim 90, wherein the modification comprises placing a transgene adjacent to an endogenous promoter in the nuclear genome.

Claim 103 (Previously Presented) The method of claim 102, wherein the promoter is a collagen gene promoter.

Claim 104 (Previously Presented) The method of claim 102, wherein the promoter is a milk protein gene promoter.

Claim 105 (Previously Presented) The method of claim 102, wherein the promoter directs expression of at least one gene in fibroblast cells.

Claim 106 (Previously Presented) The method of claim 90, wherein the modification comprises placing a marker gene at the endogenous locus in the nuclear genome.

Claim 107 (Previously Presented) The method of claim 106, wherein the marker gene is a gene that confers resistance to a drug.

Claim 108 (Previously Presented) The method of claim 107, wherein the gene that confers resistance to a drug is selected from the group consisting of neomycin, G418, hygromycin, zeocin, blasticidin and histidinol.

Claim 109 (Previously Presented) The method of claim 106, wherein the marker gene is selected from the group consisting of HPRT, gpt, a visible marker gene and a gene that can be detected with a single chain antibody/hapten system.

Claim 110 (Previously Presented) The method of claim 109, wherein the visible marker gene is GFP.

Claim 111-112 (Canceled)

Claim 113 (Currently Amended) The method of claim 90, wherein the modification homologous recombination is mediated by lipofection.

Claims 114-117 (Canceled)

Claim 118 (Previously Presented) The method of claim 90, wherein the cell is an epithelial cell, a fibroblast cell, an endothelial cell or a muscle cell.

Claim 119 (Previously Presented) The method of claim 90, wherein the cell is a G₀ cell.

Claim 120 (Previously Presented) The method of claim 119, wherein the G₀ cell is obtained by serum starvation of a cell.

Claim 121 (Currently Amended) The method of claim 62 or 90, wherein the modification homologous recombination is mediated by electroporation.

Claim 122 (Currently Amended) The method of claim 62 or 90, wherein the modification homologous recombination is mediated by transfection.

Claim 123 (Previously Presented) The method of claim 66, wherein the gene that is inactivated is α -1,3 galactosyltransferase.

Claim 124 (Previously Presented) The method of claim 99, wherein the gene that is inactivated is α -1,3 galactosyltransferase.

Claim 125 (Previously Presented) The method of claim 62 or 90, wherein the endogenous locus is an immunoglobulin gene.

Claims 126-130 (Canceled)

Claim 131 (Currently Amended) A method for producing a non-human transgenic mammal, the method comprising:

- (a) modifying the nuclear genome of a fibroblast cell that has a sufficient lifespan to be useful for genetic modification, wherein the genome has a normal karyotype, at an endogenous locus ~~by homologous recombination~~;
- (b) accomplishing successful nuclear transfer to produce the non-human transgenic mammal.

Claims 132 (Canceled)

Claim 133 (Currently Amended) A method for producing transgenic offspring from a transgenic mammal, the method comprising:

- (a) modifying the nuclear genome of a transgenic fibroblast cell that has a sufficient lifespan to be useful for genetic modification, wherein the genome has a normal karyotype, at an endogenous locus ~~by homologous recombination~~;

- (b) transferring the modified nuclear genome of the fibroblast cell to an oocyte, two cell embryo or zygote all of which have been enucleated which is capable of producing a viable nuclear transfer unit;
- (c) activating the nuclear transfer unit thereby producing an embryo;
- (d) transferring the embryo to a final surrogate mother which is a suitable host for the mammal to be grown to term;
- (e) allowing the embryo to mature.

Claim 134 (New) The method of claim 62, wherein the transgenic mammal possesses multiple genetic modifications of the nuclear genome of the fibroblast cell.

Claim 135 (New) The method of claim 62, wherein the transgenic mammal possesses one genetic modification of the nuclear genome of the fibroblast cell.

Claim 136 (New) The method of claim 134, wherein at least one genetic modification comprises removing or inactivating the genetic material and introducing a transgene.

Claim 137 (New) The method of claim 134, wherein the multiple genetic modifications occur simultaneously.

Claim 138 (New) The method of claim 134, wherein the multiple genetic modifications occur subsequently.

Claim 139 (New) The method of claim 134, wherein the multiple genetic modifications occur sequentially.

Claim 140 (New) The method of claim 134, wherein there is more than two genetic modifications of the nuclear genome of the fibroblast cell.

Claim 141 (New) The method of claim 62, wherein cells from the embryo are used for further rounds of nuclear transfer, wherein additional genetic modifications are introduced prior to further rounds of nuclear transfer.

Claim 142 (New) The method of claim 141, wherein cells from the fetus are used for further rounds of nuclear transfer, wherein the additional genetic modifications are introduced prior to further rounds of nuclear transfer.

Claim 143 (New) The method of claim 141, wherein cells from the adult are used for further rounds of nuclear transfer, wherein the additional genetic modifications are introduced prior to further rounds of nuclear transfer, and wherein the adult comprises an animal from birth onwards.

Claim 144 (New) The method of claim 62, wherein modification of the nuclear genome places a transgene at a site which places the transgene under the control of an endogenous regulatory region.

Claim 145 (New) The method of claim 144, wherein the endogenous regulatory region comprises a promoter.

Claim 146 (New) The method of claim 144, wherein the endogenous regulatory comprises the polyadenylation site.

Claim 147 (New) The method of claim 145, wherein the promoter comprises a milk gene promoter.

Claim 148 (New) The method of claim 145, wherein the promoter comprises a collagen gene promoter.

Claim 149 (New) The method of claim 62, wherein the modification of the nuclear genome of a fibroblast cell is by homologous recombination.

Claim 150 (New) The method of claim 90, wherein the modification of the nuclear genome of a fibroblast cell is by homologous recombination.

Claim 151 (New) The method of claim 131, wherein the modification of the nuclear genome of a fibroblast cell is by homologous recombination.

Claim 152 (New) The method of claim 133, wherein the modification of the nuclear genome of a transgenic fibroblast cell is by homologous recombination.